Please amend the specification in adherence with rules 37 C.F.R. § 1.821-1.825 as follows:

IN THE SPECIFICATION:

Please replace paragraph beginning at page 5, line 15, with the following rewritten paragraph:

— In accordance with the objects outlined above, the present invention provides non-naturally occurring insulin activity (IA) proteins (e.g. the proteins are not found in nature) comprising amino acid sequences that are less than about 98% identical to human insulin. The IA proteins have at least one altered biological property of an insulin protein; for example, the IA proteins will be more stable than insulin and bind to a cell comprising an insulin receptor. Thus, the invention provides IA proteins with amino acid sequences that have at least about 1-20 amino acid substitutions as compared to the human insulin sequence shown in Figure 1B (SEQ ID NO:2).—

Please replace the section titled "BRIEF DESCRIPTION OF THE DRAWINGS", beginning on page 6, line 21, with the following rewritten section:

— Figure 1A (SEQ ID NO:1) depicts the amino acid sequence of the insulin precursor (GenBank accession #P01308, #AAA59173). Amino acid residues 1-24 represent the signal peptide; amino acid residues 25-54 represent the mature B-chain; amino acid residues 90-110 represent the mature A-chain.

Figure 1B (SEQ ID NO:2) depicts the amino acid sequence of human insulin [GenBank accession #229122; Nicol and Smith, Nature 187:483-485 (1960)], which is used herein for PDA design and for reference of amino acid positions. The A-chain comprises amino acid residues 1-21 (sometimes referred to as A1 through A 21) and the B-chain comprises residues 22-51 (sometimes referred to as B1 through B30), respectively.

Figure 1C depicts the amino acid sequences of the A-chains of human insulin (1TRZ:A and 1TRZ:C; SEQ ID NOS:3 & 5) and B-chains of human insulin (1TRZ:B and 1TRZ:D; SEQ ID NOS:4 & 6) as used in determination of the structure of insulin (T3R3) complex with two zinc ions [PDB entry 1TRZ; Ciszak and Smith, Biochemistry 33(6):1512-7(1994)] and secondary structure elements. Secondary structure element legend: H, alpha helix (4-helix); B, residue in isolated beta bridge; E, extended strand, participates in beta ladder; G, 310 helix (3-helix); I, pi helix (5-helix); T, hydrogen bonded turn; S, bend.

Figure 2A depicts the structure of a wild type insulin monomer with side chains for disulfide bonds (A6-A11, A7-B7, and A20-B19) and the B-Ala14 side chain shown.

Figure 2B depicts the structure of a wild type insulin hexamer.

Figure 2C depicts a closeup of the B14, B5 design region in the insulin hexamer.

Figure 3 shows preferred IA protein sequences from PDA designs involving disulfide replacement. Amino acid changes when compared to wild type human insulin are indicated in bold and are underlined.

Figure 3A (SEQ ID NO:7) shows a preferred IA protein sequence from PDA design 'cys1'.

Figure 3B (SEQ ID NO:8) shows a preferred IA protein sequence from PDA design 'cys77a'.

Figure 3C (SEQ ID NO:9) shows a preferred IA protein sequence from PDA design 'cys77b'.

Figure 3D (SEQ ID NO:10) shows a preferred IA protein sequence from PDA design 'cys77d'.

Figure 3E (SEQ ID NO:11) shows a preferred IA protein sequence from PDA design 'cys77d+'.

Figure 3F (SEQ ID NO:12) shows a preferred IA protein sequence from PDA design 'helix 24'.

Figure 3G (SEQ ID NO:13) shows a preferred IA protein sequence from PDA design 'cys-4'. For this design, a "-" in the sequence indicates a deletion.

Figures 4A–4G (SEQ ID NOS:14-20) show preferred IA protein sequences from PDA designs involving mutations which promote insulin hexamer formation. Amino acid changes when compared to wild type human insulin are indicated in bold and are underlined.

Figures 5A-5C (SEQ ID NOS:21-23) show preferred IA protein sequences from PDA designs involving global redesigns for improved stability. Amino acid changes when compared to wild type human insulin are indicated in bold and are underlined.

Figure 5A (SEQ ID NO:21) shows a preferred IA protein sequence from PDA design 'trz_06'.

Figure 5B (SEQ ID NO:22) shows a preferred IA protein sequence from PDA design 'trz_7b'.

Figure 5C (SEQ ID NO:23) shows a preferred IA protein sequence from PDA design 'trz_08'.

Figure 6 depicts the synthesis of a full-length gene and all possible mutations by PCR. Overlapping oligonucleotides corresponding to the full-length gene (black bar, Step 1) and comprising one or more

desired mutations are synthesized, heated and annealed. Addition of DNA polymerase to the annealed oligonucleotides results in the 5' to 3' synthesis of DNA (Step 2) to produce longer DNA fragments (Step 3). Repeated cycles of heating, annealing, and DNA synthesis (Step 4) result in the production of longer DNA, including some full-length molecules. These can be selected by a second round of PCR using primers (indicated by arrows) corresponding to the end of the full-length gene (Step 5).

Figure 7 depicts a preferred scheme for synthesizing an IA protein library of the invention. The wild type gene, or any starting gene, such as the gene for the global minima gene, can be used. Oligonucleotides comprising sequences that encode different amino acids at the different variant positions (indicated in the Figure by box 1, box 2, and box 3) can be used during PCR. Those primers can be used in combination with standard primers. This generally requires fewer oligonucleotides and can result in fewer errors.

Figures 8A and 8B depict an overlapping extension method. At the top of Figure 8A is the template DNA showing the locations of the regions to be mutated (black boxes) and the binding sites of the relevant primers (arrows). The primers R1 and R2 represent a pool of primers, each containing a different mutation; as described herein, this may be done using different ratios of primers if desired. The variant position is flanked by regions of homology sufficient to get hybridization. Thus, as shown in this example, oligos R1 and F2 comprise a region of homology and so do oligos R2 and F3. In this example, three separate PCR reactions are done for step 1. The first reaction contains the template plus oligos F1 and R1. The second reaction contains template plus oligos F2 and R2, and the third contains the template and oligos F3 and R3. The reaction products are shown. In Step 2, the products from Step 1 tube 1 and Step 1 tube 2 are taken. After purification away from the primers, these are added to a fresh PCR reaction together with F1 and R4. During the denaturation phase of the PCR, the overlapping regions anneal and the second strand is synthesized. The product is then amplified by the outside primers, F1 and R4. In Step 3, the purified product from Step 2 is used in a third PCR reaction, together with the product of Step 1, tube 3 and the primers F1 and R3. The final product corresponds to the full length gene and contains the required mutations. Alternatively, Step 2 and Step 3 can be performed in one PCR reaction.

Figures 9A and 9B depict a ligation of PCR reaction products to synthesize the libraries of the invention. In this technique, the primers also contain an endonuclease restriction site (RE), either generating blunt ends, 5' overhanging ends or 3' overhanging ends. We set up three separate PCR reactions for Step 1. The first reaction contains the template plus oligos F1 and R1. The second reaction contains

template plus oligos F2 and R2, and the third contains the template and oligos F3 and R3. The reaction products are shown. In Step 2, the products of Step 1 are purified and then digested with the appropriate restriction endonuclease. The digestion products from Step 2, tube 1 and Step 2, tube 2 are ligated togther with DNA ligase (Step 3). The products are then amplified in Step 4 using oligos F1 and R4. The whole process is then repeated by digesting the amplified products, ligating them to the digested products of Step 2, tube 3, and then amplifying the final product using oligos F1 and R3. It would also be possible to ligate all three PCR products from Step 1 together in one reaction, providing the two restriction sites (RE1and RE2) were different.

Figure 10 depicts blunt end ligation of PCR products. In this technique, oligos such as F2 and R1 or R2 and F3 do not overlap, but they abut. Again three separate PCR reactions are performed. The products from tube 1 and tube 2 (see Figure 9A, Step 1) are ligated, and then amplified with outside primers F1 and R4. This product is then ligated with the product from Step 1, tube 3. The final products are then amplified with primers F1 and R3. —

In the section titled "DETAILED DESCRIPTION OF THE INVENTION, " please replace paragraph beginning at page 22, line 12, with the following rewritten paragraph:

– In one aspect of this embodiment, the IA protein of the invention has at least one different residue from the human insulin sequence. Preferred IA protein sequences comprising a substitution of one amino acid residue are shown in Figures 4B, 4C, 4D, 4F, and 4G (SEQ ID NOS:15-17, 19 & 20).–

Please replace paragraph beginning at page 22, line 15, with the following rewritten paragraph:

– In another aspect of this embodiment, the IA protein of the invention has at least two different residues from the human insulin sequence. Preferred IA protein sequences comprising a substitution of two amino acid residues are shown in Figures 3C, 3F, 4A, and 4E (SEQ ID NOS:9, 12, 14 & 18).–

Please replace paragraph beginning at page 22, line 18, with the following rewritten paragraph:

– In another aspect of this embodiment, the IA protein of the invention has at least three different residues from the human insulin sequence. A preferred IA protein sequence comprising a substitution of three amino acid residues is shown in Figure 3E (SEQ ID NO:11).–

Please replace paragraph beginning at page 22, line 21, with the following rewritten paragraph:

– In another aspect of this embodiment, the IA protein of the invention has at least four different residues from the human insulin sequence. Preferred IA protein sequences comprising a substitution of four amino acid residues are shown in Figures 3C, 3F, 4A, and 4E (SEQ ID NOS:9, 12, 14 & 18).–

Please replace paragraph beginning at page 22, line 26, with the following rewritten paragraph:

– In another aspect of this embodiment, the IA protein of the invention has at least six different residues from the human insulin sequence. A preferred IA protein sequence comprising a substitution of six amino acid residues is shown in Figure 5A (SEQ ID NO:21). A preferred IA protein sequence comprising a substitution of two amino acid residues and a deletion of four amino acid residues is shown in Figure 3G (SEQ ID NO:13).–

Please replace paragraph beginning at page 23, line 15, with the following rewritten paragraph:

– In another aspect of this embodiment, the IA protein of the invention has at least fourteen different residues from the human insulin sequence. A preferred IA protein sequence comprising a substitution of fourteen amino acid residues is shown in Figure 5B (SEQ ID NO:22).–

Please replace paragraph beginning at page 23, line 20, with the following rewritten paragraph:

– In another aspect of this embodiment, the IA protein of the invention has at least sixteen different residues from the human insulin sequence. A preferred IA protein sequence comprising a substitution of sixteen amino acid residues is shown in Figure 5C (SEQ ID NO:23). –

Please replace paragraph beginning at page 23, line 23, with the following rewritten paragraph:

– In another aspect of this embodiment, the IA protein of the invention has at least twenty different residues from the human insulin sequence. A preferred IA protein sequence comprising a substitution of twenty amino acid residues is shown in Figure 3A (SEQ ID NO:7).–

Please replace paragraph beginning at page 27, line 5, with the following rewritten paragraph:

– The insulin may be from any number of organisms, with insulins from mammals being particularly preferred. Suitable mammals include, but are not limited to, rodents (rats, mice, hamsters, guinea pigs, etc.), primates, farm animals (including sheep, goats, pigs, cows, horses, etc) and in the most preferred embodiment, from humans (the sequence of which is depicted in Figure 1B (SEQ ID NO:2). As will be appreciated by those in the art, insulins based on insulins from mammals other than humans may find use in animal models of human disease. The GenBank accession numbers for a variety of mammalian insulin species is as follows: bovine, IPBO; dog, IPDG; sheep, INSH; cat, INCT; pig, IPPG; mouse, INMS1, INMS2; rat, IPRT1, IPRT2; horse, IPHO; rabbit, INRB; guinea pig, IPGP; hamster, INHY; goat, INGT, chimpanzee, A42179; green monkey, B42179; and human IPHU.–

Please replace paragraph beginning at page 32, line 9, with the following rewritten paragraph:

– The IA proteins and nucleic acids of the invention are distinguishable from naturally occurring insulins. By "naturally occurring" or "wild type" or grammatical equivalents, herein is meant an amino acid sequence or a nucleotide sequence that is found in nature and includes allelic variations; that is, an amino acid sequence or a nucleotide sequence that usually has not been intentionally modified. Accordingly, by "non-naturally occurring" or "synthetic" or "recombinant" or grammatical equivalents thereof, herein is meant an amino acid sequence or a nucleotide sequence that is not found in nature; that is, an amino acid sequence or a nucleotide sequence that usually has been intentionally modified. It is understood that once a recombinant nucleic acid is made and reintroduced into a host cell or organism, it will replicate non-recombinantly, i.e., using the *in vivo* cellular machinery of the host cell rather than *in vitro* manipulations, however, such nucleic acids, once produced recombinantly, although subsequently replicated non-recombinantly, are still considered recombinant for the purpose of the invention. A representative amino acid sequence of a naturally occurring human insulin is shown in Figure 1B (SEQ ID NO:2). It should be noted that unless otherwise stated, all positional numbering of IA proteins and IA

nucleic acids is based on this sequence. That is, as will be appreciated by those in the art, an alignment of insulin proteins and IA proteins can be done using standard programs, as is outlined below, with the identification of "equivalent" positions between the two proteins. Thus, the IA proteins and nucleic acids of the invention are non-naturally occurring; that is, they do not exist in nature.–

Please replace paragraph beginning at page 32, line 27, with the following rewritten paragraph:

– Thus, in a preferred embodiment, the IA protein has an amino acid sequence that differs from a wild-type insulin sequence by at least 2% of the residues. That is, the IA proteins of the invention are less than about 98% identical to an insulin amino acid sequence. Accordingly, a protein is an "IA protein" if the overall homology of the protein sequence to the amino acid sequence shown in Figure 1A or Figure 1B (SEQ ID NOS:1 or 2) is preferably less than about 98%, more preferably less than about 95%, even more preferably less than about 90% and most preferably less than 85%. In some embodiments the homology will be as low as about 75 to 80%. In other embodiments the homology will be as low 50-70%. Stated differently, based on the human insulin sequence of 51 residues (see Figure 1B; SEQ ID NO:2), IA proteins have at least about 1 residue that differs from the human insulin sequence (2%), with IA proteins having from 2 residues to upwards of 25 residues being different from the human insulin sequence. Preferred IA proteins have 1-20 different residues with from about 2 to about 10 being particularly preferred (that is, 4-20% of the protein is not identical to human insulin).–

Please replace paragraph beginning at page 34, line 16, with the following rewritten paragraph:

– The alignment may include the introduction of gaps in the sequences to be aligned. In addition, for sequences which contain either more or fewer amino acids than the protein of Figure 1B (SEQ ID NO:2), it is understood that in one embodiment, the percentage of sequence identity will be determined based on the number of identical amino acids in relation to the total number of amino acids. Thus, for example, sequence identity of sequences shorter than that shown in Figure 1B, as discussed below, will be determined using the number of amino acids in the shorter sequence, in one embodiment. In percent identity calculations relative weight is not assigned to various manifestations of sequence variation, such as, insertions, deletions, substitutions, etc.–

Please replace paragraph beginning at page 34, line 30, with the following rewritten paragraph:

– Thus, IA proteins of the present invention may be shorter or longer than the amino acid sequence shown in Figure 1B (SEQ ID NO:2). Thus, in a preferred embodiment, included within the definition of IA proteins are portions or fragments of the sequences depicted herein. Fragments of IA proteins are considered IA proteins if a) they share at least one antigenic epitope; b) have at least the indicated homology; c) and preferably have IA biological activity as defined herein.–

Please replace paragraph beginning at page 35, line 18, with the following rewritten paragraph:

– Human insulin core residues are as follows: positions A2, A3, A16, B11, B15, and B24, whereby "A" refers to a residue in the A-chain of insulin and the number identifies the position within the A-chain. Accordingly, "B" refers to a residue in the B-chain of insulin and the number identifies the position within the B-chain. In the context of the mature insulin, the A-chain comprises residues 1-21 and the B-chain residues 22-51 of the amino acid sequence shown in Figure 1B (SEQ ID NO:2). In some embodiments, when referred explicitly to the B-chain, residues 22-51 are also referred to B1 - B30, respectively. Accordingly, in a preferred embodiment, IA proteins have variable positions selected from positions A2, A3, A16, B11, B15, and B24.–

Please replace paragraph beginning at page 37, line 11, with the following rewritten paragraph:

– In a preferred aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 5A (SEQ ID NO:21). This sequence shows 6 amino acid substitution (11-12% divergence from the wild type insulin sequence) and comprises A1-N, A10-Q, A16-Y, B1-D, B25-N, and B27-D.–

Please replace paragraph beginning at page 37, line 14, with the following rewritten paragraph:

– In another aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 5B (SEQ ID NO:22). This sequence shows 14 mutation (27-28% divergence from the wild type insulin sequence) and comprises A1-N, A10-Q, A16-Y, A17-Y, A19-F, B1-D, B2-K, B4-F, B11-I, B12-R, B14-W, B25-N, B26-F, and B27-D.–

Please replace paragraph beginning at page 37, line 18, with the following rewritten paragraph:

– In one preferred aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 5C (SEQ ID NO:23). This sequence shows 16 mutation (31-34% divergence from the wild type insulin sequence) and comprises A1-N, A10-Q, A16-Y, A17-Y, A19-F, B1-D, B2-K, B4-F, B8-L, B11-I, B12-R, B14-W, B25-N, B26-F, B27-D, and B28-N.–

Please replace paragraph beginning at page 38, line 8, with the following rewritten paragraph:

– In one aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 3A (SEQ ID NO:7). This sequence shows 20 mutation (39-40% divergence from the wild type insulin sequence) and comprises A1-N, A2-I, A6-A, A7-S, A10-Q, A11-A, A16-I, A17-Y, A19-F, A20-D, B1-D, B4-F, B7-Y, B11-I, B12-R, B14-W, B19-A, B25-N, B26-F, and B27-D.–

Please replace paragraph beginning at page 38, line 21, with the following rewritten paragraph:

– In one aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 3B (SEQ ID NO:8). This sequence shows 4 mutation (8% divergence from the wild type insulin sequence) and comprises A7-S, B2-E, B4-Y, and B7-Y.–

Please replace paragraph beginning at page 38, line 24, with the following rewritten paragraph:

– In another aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 3C (SEQ ID NO:9). This sequence shows 2 mutation (8% divergence from the wild type insulin sequence) and comprises A7-S, and B7-D.–

Please replace paragraph beginning at page 38, line 27, with the following rewritten paragraph:

– In a preferred aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 3D (SEQ ID NO:10). This sequence shows 4 mutation (8% divergence from the wild type insulin sequence) and comprises A7-S, B2-T, B4-Y, and B7-Y.–

Please replace paragraph beginning at page 39, line 1, with the following rewritten paragraph:

– In another aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 3E (SEQ ID NO:11). This sequence shows 3 mutation (6% divergence from the wild type insulin sequence) and comprises A7-S, B4-Y, and B7-Y.–

Please replace paragraph beginning at page 39, line 4, with the following rewritten paragraph:

– In one aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 3F (SEQ ID NO:12). This sequence shows 2 mutation (4% divergence from the wild type insulin sequence) and comprises A7-S, B7-E.–

Please replace paragraph beginning at page 39, line 7, with the following rewritten paragraph:

– In another preferred aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 3G (SEQ ID NO:13). This sequence shows 2 mutation and 4deletions at positions B1 to B4 (12% divergence from the wild type insulin sequence) and comprises A7-E and B7-E.–

Please replace paragraph beginning at page 40, line 9, with the following rewritten paragraph:

– In one aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 4C (SEQ ID NO:16). This sequence shows only 1 mutation (2% divergence from the wild type insulin sequence) and comprises B14-F. This IA protein does not bind efficiently a phenol preservative, however, it still forms a hexamer.–

Please replace paragraph beginning at page 40, line 13, with the following rewritten paragraph:

– In another aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 4D (SEQ ID NO:17). This sequence shows only 1 mutation (2% divergence from the wild type insulin sequence) and comprises B14-W. This IA protein does not bind efficiently a phenol preservative, however, it still forms a hexamer.–

Please replace paragraph beginning at page 40, line 17, with the following rewritten paragraph:

– In another aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 4F (SEQ ID NO:19). This sequence shows only 1 mutation (2% divergence from the wild type insulin sequence) and comprises B14-Y. This IA protein does not bind efficiently a phenol preservative, however, it still forms a hexamer.–

Please replace paragraph beginning at page 40, line 21, with the following rewritten paragraph:

– In another aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 4G (SEQ ID NO:20). This sequence shows only 1 mutation (2% divergence from the wild type insulin sequence) and comprises B14-I. This IA protein does not bind efficiently a phenol preservative, however, it still forms a hexamer.–

Please replace paragraph beginning at page 40, line 26, with the following rewritten paragraph:

– In one aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 4B (SEQ ID NO:15). This sequence shows only 1 mutation (2% divergence from the wild type insulin sequence) and comprises B5-F. This IA protein does not bind efficiently a phenol preservative, however, it still forms a hexamer.–

Please replace paragraph beginning at page 41, line 3, with the following rewritten paragraph:

– In one aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 4A (SEQ ID NO:14). This sequence shows 2 mutations (42% divergence from the wild type insulin sequence) and comprises B5-F and B14-F. This IA protein does not bind efficiently a phenol preservative, however, it still forms a hexamer.–

Please replace paragraph beginning at page 41, line 7, with the following rewritten paragraph:

– In another aspect of this embodiment, the IA protein comprises the amino acid sequence shown in Figure 4E (SEQ ID NO:18). This sequence shows 2 mutations (42% divergence from the wild type insulin sequence) and comprises B5-F and B14-W. This IA protein does not bind efficiently a phenol preservative, however, it still forms a hexamer.–

Please replace paragraph beginning at page 68, line 31, with the following rewritten paragraph:

– Thus, any protein sequence showing mutations at the positions according to Table 1 will potentially generate a more stable and active IA protein. In particular those protein sequences found among the list of the lowest 101 MC generated sequences (data not shown) have a high potential to result in a more stable and active IA protein. A preferred IA sequence derived from the PDA design 'cys1' is shown in Figure 3A (SEQ ID NO:7). This sequence shows 20 mutations when compared to the wild type insulin: G-A1-N, I-A2-L, C-A6-A, C-A7-S, I-A10-Q, C-A11-A, L-A16-I, E-A17-Y, Y-A19F, C-A20-D, F-B1-D, Q-B4-F, C-B7-Y, L-B11-I, V-B12-R, A-B14-W, C-B19-A, F-B25-N, Y-B26-F, and T-B27-D. Cysteines at positions A6, A11, and B19 all become Ala, indicating a lack of space at these positions.–

Please replace paragraph beginning at page 69, line 25, with the following rewritten paragraph:

– Thus, any protein sequence showing mutations at the positions according to Table 2 will potentially generate a more stable and active IA protein. In particular those protein sequences found among the list of the lowest 101 MC generated sequences (data not shown) have a high potential to result in a more stable and active IA protein. A preferred IA sequence derived from the PDA design 'cys77a' is shown in Figure 3B (SEQ ID NO:8). This sequence shows 4 mutations when compared to the wild type insulin: C-A7-S, V-B2-E, Q-B4-Y, and C-B7-Y.–

Please replace paragraph beginning at page 70, line 3, with the following rewritten paragraph:

– PDA design 'cys77b' is similar to PDA design 'cys77a', however, in this calculation only positions A7 and B7 were allowed to change to other residues. The other positions had their amino acid identities fixed, but were allowed to change conformation. 'Cys77b 'was a design of only A7-B7, the reduced conformational freedom blocked the Tyr mutation from B7. A preferred sequence from this design is shown in Figure 3C (SEQ ID NO:9). This sequence shows 2 mutations, C-A7-S and C-B7-D.–

Please replace paragraph beginning at page 70, line 8, with the following rewritten paragraph:

– PDA designs 'cys77d' and 'cys77d+ ' are the minimal sets of mutations that allow the A7 Ser, B7 Tyr pair to occur. Preferred sequences from these two designs are shown in Figures 3D and 3E (SEQ ID NOS:10 &11).–

Please replace paragraph beginning at page 70, line 10, with the following rewritten paragraph:

– The sequence shown in Figure 3D (SEQ ID NO:10) shows 4 mutations, C-A7-S , V-B2-T, Q-B4-Y, and C-B7-Y.–

Please replace paragraph beginning at page 70, line 11, with the following rewritten paragraph:

– The sequence shown in Figure 3E (SEQ ID NO:11) shows 3 mutations, C-A7-S , Q-B4-Y, and C-B7-Y.–

Please replace paragraph beginning at page 70, line 14, with the following rewritten paragraph:

– A preferred sequence obtained from this design is shown in Figure 3F (SEQ ID NO:12). This sequence shows 2 mutations, C-A7-S and C-B7-E.–

Please replace paragraph beginning at page 70, line 17, with the following rewritten paragraph:

– A preferred sequence obtained from this design is shown in Figure 3G (SEQ ID NO:13). This sequence shows 2 substitutions, C-A7-E and C-B7-E and deletions of residues at positions B1 to B4. This IA protein generates moreroom for A7-B7.–

Please replace paragraph beginning at page 72, line 12, with the following rewritten paragraph:

– Preferred IA sequences obtained from this PDA calculation and comprising only B14 substitutions are shown in Figures 4C, 4D, 4F, and 4G (SEQ ID NOS:16-17 & 19-20).–

Please replace paragraph beginning at page 72, line 17, with the following rewritten paragraph:

– Other substitutions at B14 with similar effects are B14Tyr (Figure 4F; SEQ ID NO:19) and B14 Ile (Figure 4G; SEQ ID NO:20). These mutations may require further mutations as described further below for B5 substitutions.–

Please replace paragraph beginning at page 72, line 30, with the following rewritten paragraph:

– A preferred IA protein sequence comprising a B5 substitution only is shown in Figure 4B (SEQ ID NO:15).–

Please replace paragraph beginning at page 73, line 6, with the following rewritten paragraph:

– Any combination of the above substitutions is possible, such as B14-Phe/B5-Phe, B14-Phe/B5-Trp, B14-Trp/B5-Phe, B14-Trp/B5-Trp, B14-Tyr/B5-Phe, B14-Tyr/B5-Trp, B14-Ile/B5-Phe, and B14-Ile/B5-Trp. Preferred IA sequences comprising B5 and B14 substitutions are shown in Figure 4A and in Figure 4E (SEQ ID NOS:14 &18). –

Please replace paragraph beginning at page 74, line 12, with the following rewritten paragraph:

– A preferred IA protein sequence from the PDA calculation 'trz_06' is shown in Figure 5A (SEQ ID NO:21). This sequence shows 6 mutations when compared to the wild type insulin sequence, G-A1-N, I-A10-Q, L-A16-Y, F-B1-D, F-B25-N, and T-B27-D.–

Please replace paragraph beginning at page 74, line 15, with the following rewritten paragraph:

– A preferred IA protein sequence from the PDA calculation 'trz_07b' is shown in Figure 5B (SEQ ID NO:22). This sequence shows 14 mutations when compared to the wild type insulin sequence, G-A1-N, I-A10-Q, L-A16-Y, E-A17-Y, Y-A19-F, F-B1-D, V-B2-K, Q-B4-F, L-B11-I, V-B12-R, A-B14-W, F-B25-N, Y-B26-F and T-B27-D.–

Please replace paragraph beginning at page 74, line 18, with the following rewritten paragraph:

– A preferred IA protein sequence from the PDA calculation 'trz_08' is shown in Figure 5C (SEQ ID NO: 23). This sequence shows 16 mutations when compared to the wild type insulin sequence, G-A1-N, I-A10-Q, L-A16-Y, E-A17-Y, Y-A19-F, F-B1-D, V-B2-K, Q-B4-F, G-B8-L, L-B11-I, V-B12-R, A-B14-W, F-B25-N, Y-B26-F, T-B27-D and P-B28-N.–